Please address all future correspondence to:

Patrea L. Pabst
Holland & Knight LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, GA 30309-3400

(404) 817-8473
(404) 817-8588 (fax)

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

In the Claims

7. (Twice Amended) The method of claim 1 wherein the molecule to be delivered is selected from the group consisting of [non-nucleic acid] drugs other than nucleic acids and proteins and diagnostic agents.

19. (Three Times Amended) The conjugate of claim 13 wherein the molecule to be delivered is a [non-nucleic acid] drug other than nucleic acids and proteins.

Remarks

Claims 1-25 are pending. Claims 7 and 19 have been amended. Claims 7 and 19 have been amended to recite "drugs other than nucleic acids and proteins". Support for these amendments can be found, for example, at page 2, lines 10-13. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The presently claimed method and composition are directed to specifically targeting a conjugate of an agent and a molecule to the large vessel endothelium. The claimed conjugate composition is formed *before* delivery to the endothelium.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 5, 6, 12 and 16-18 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Applicants submit an article by Baumgartner *et. al.* (*Circulation*, March 31, 1998, 97(12)1114-1123) which teaches therapeutic angiogenesis via intramuscular gene transfer using naked plasmid DNA encoding an endothelial cell mitogen. Baumgartner thus clearly illustrates successful gene therapy to endothelial cells. Additionally, an abstract is submitted (Nguyen *et al., Cancer Gene Ther.*, 1997, May-June) which discloses the use of adenoviral protein particles that were *chemically modified by covalent attachment of poly-L-lysine to the viral protein capsid. In vitro* and *in vivo* results are provided within the abstract. Furthermore, Watanabe *et al.* (*Nippon Rinsho*, March 1998, 56(3):724-730) teach a method that incorporates the use of molecules conjugated to receptor ligands (ligands for the transferrin receptor) via biotin and streptavidin. The transferrin receptor on human cancer cells internalizes the ligand conjugated to the molecule of interest. Transferrin has also been identified in screens to identify targeting ligands to myogenic cells (Feero *et al., Gene Ther.*, 1997, 4(7)664-674). Transferrin was shown to mediate cell specific transfer of poly-L-lysine condensed DNA (Feero *et al., Gene Ther.*, 1997, 4(7)664-674). Finally, Lode *et al.* (*Proc. Natl. Acad. Sci.*, Vol. 95, pp. 2475-2480, March

1998), characterize, in part, the state gene therapy as it directly relates to the presently claimed method and composition. Lode *et al* teach the vaccination with a fusion protein, constructed via a linker peptide, which induces a T cell-mediated immunity that protects mice from challenge with tumor cells. The results clearly demonstrate the efficacy of a gene therapy approach using a genetically engineered fusion protein, fused via a linker protein.

The Examiner states that "a reliance upon the teachings of those skilled in the art is insufficient to overcome a rejection based upon the alleged unpredictability of the presently claimed method and composition. However, the predictability, or lack thereof, in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 369-370 (CCPA 1971). The Applicants respectfully submit that the foregoing citations and references provide evidence demonstrating that those skilled in the art of genetic delivery were able to transfer fusion proteins, covalently modified proteins, molecules conjugated to receptor ligands, and cell specific nucleic acid/receptor ligand conjugates. Furthermore, well established methods were used to identify ligands to be used as mediators of cell specific delivery. In addition, as taught by Baumgartner *et al.*, the transfer of naked DNA to endothelial cells had been accomplished with success.

The Applicants respectfully submit that one of skill would not have to endure undue experimentation to practice the claimed method and composition. The Applicants have established via the enclosed references that 1) endothelial cells are amenable to gene therapy; 2) conjugated ligands used to direct molecules of interest to EPCR may be readily obtained using

screening methods available at the time of filing the present application; 3) the transfer of proteins, modified and unmodified, was well established in the art; and 4) receptor ligands had been readily used to direct molecules of interest to specific cellular targets. It should be noted that Baumgartner *et al.* specifically interpret their data to "indicate that intramuscular injection of naked plasmid DNA achieves constitutive overexpression of VEGF sufficient to induce therpeutic angiogenesis in selected patients with critical limb ischemia."

Claims 7 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner stated that amending claims 7 and 19 to read "drugs other than nucleic acids and proteins" would be acceptable. Applicants have amended the claims per the Examiner's suggestion.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 7 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

In view of the amendments to claims 7 and 19, the Applicants respectfully submit that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn. Proper support for the amendment can be found, for example, at page 2, lines 10-13.

Rejection Under 35 U.S.C. § 102

Claims 13, 15, 19, and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,254,532 to Schwarz ("Schwarz"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Schwarz teaches at column 2, lines 21-23, purified protein S in combination with activated protein C being immobilized at the surfaces of *artificial* vessels to prevent thrombosing. The Examiner asserts that according to Fukudome (U.S. Patent No. 5,852,171), protein S and activated protein C are inherently conjugated when bound to EPCR on large vessel endothelial cells. However, Fukudome goes on to state at lines 48-49 that protein S binding to a protein C/EPCR complex is *not* cell specific. The claims, as presently pending, are drawn to a method for *selectively* delivering molecules to the nucleus of endothelial cells. Additionally, base claim 13 teaches that the conjugate is formed *before* delivery to a large vessel endothelial cell. Schwarz teaches in Example 10 that protein S and protein C are added in a combined application, but do not teach a conjugation of protein S and protein C. Fukudome teaches, at lines 45-47 of column 2, the binding of protein S to the APC/protein C on negatively charged surfaces, suggesting that APC/protein C must be on the negatively charged surface as a prerequisite for protein S binding. Therefore, neither Schwarz or Fukudome, teach a conjugate of an agent and a molecule *to be delivered* to a large vessel endothelial cell.

U.S.S.N. 09/139,425
Filed: August 25, 1998
AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1-25 is respectfully solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: February 4, 2002

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: February 4, 2002

U.S.S.N. 09/139,425
Filed: August 25, 1998
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (three times amended) A method for selectively delivering molecules to the nucleus of endothelial cells of the large vessels, comprising

administering a conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) and the molecule to be delivered to large vessel endothelial cells, wherein the molecules are delivered to the nucleus of the large vessel endothelial cells.

2. The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and an antibody to EPCR.

3. The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and activated protein C.

4. The method of claim 1 wherein the conjugate comprises a chimeric antibody binding to the molecule to be delivered and to EPCR.

5. (four times amended) The method of claim 1 wherein the molecule to be delivered is a nucleic acid molecule and the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell and the nucleic acid molecule is delivered by directly contacting the endothelial cells of large vessels with the nucleic acid molecule conjugate or by catherization to the endothelial cells.

6. (twice amended) The method of claim 5 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

7. (Twice Amended) The method of claim 1 wherein the molecule to be delivered is selected from the group consisting of [non-nucleic acid] drugs other than nucleic acids and proteins and diagnostic agents.

8. The method of claim 1 wherein the molecule to be delivered is a protein.

9. The method of claim 8 wherein the protein is a transcription factor.

10. The method of claim 1 wherein the molecule to be delivered is coupled to the agent which binds to EPCR by molecules selected from the group consisting of steptavidin and biotin, and molecules having multiple positive charges.

11. The method of claim 1 wherein the conjugate is administered to large vessel endothelial cells in culture or isolated from an individual.

12. (amended) The method of claim 1 wherein the conjugate is administered directly to the cells of to an individual in need of treatment or diagnosis.

13. (amended) A conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of protein C, activated protein C, antibodies reactive with EPCR and fragments thereof binding to EPCR, and a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label, wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

14. The conjugate of claim 13 wherein the conjugate is formed with an antibody to EPCR, or a fragment or recombinant molecule based thereon, binding to EPCR.

15. The conjugate of claim 13 wherein the conjugate is formed between the agent to be delivered and activated protein C.

16. (four times amended) The conjugate of claim 13 wherein the molecule to be delivered is a nucleic acid molecule in combination with means for directly contacting the nucleic acid molecule conjugate directly with the endothelial cells of large vessels, wherein the means are for in vitro treatment of the cells or by catherization to the endothelial cells.

17. (twice amended) The conjugate of claim 16 wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell.

18. (twice amended) The conjugate of claim 16 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

19. (Three Times Amended) The conjugate of claim 13 wherein the molecule to be delivered is a [non-nucleic acid] drug other than nucleic acids and proteins.

20. The conjugate of claim 13 wherein the molecule to be delivered is a protein.

21. The conjugate of claim 20 wherein the protein is a transcription factor.

22. The conjugate of claim 20 comprising a coupling means which binds the molecule to be delivered to the agent which binds EPCR.

22. The conjugate of claim 22 wherein the coupling means is a positively charged polymer or molecule.

24. The conjugate of claim 22 wherein the coupling means is streptavidin-biotin.

25. The conjugate of claim 13 comprising a chimeric antibody which binds to EPCR and to the molecule to be delivered.